REMARKS/ARGUMENTS

By the present amendment, claims 9, 11 and 19 have been amended as described below. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application. No new matter has been entered by the present amendment and its entry is respectfully requested.

The office action dated October 29, 2008 has been carefully considered. It is believed that the amendments and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Restriction/Election

We confirm that Applicant has elected the Group I invention comprising claims 1-20. Consequently, claims 21-29 have been withdrawn. However, we disagree with the Examiner that claims 6 and 15 should be withdrawn as they do not relate to a non-elected invention, but rather a non-elected species. Further, for the reasons discussed below, Applicant respectfully submits that claims 1-20 are novel and inventive over the cited references and thus, claims directed to non-elected species should not be withdrawn.

35 USC §112, first paragraph

The Examiner rejected claims 1-5, 7-14 and 16-20 under 35 USC §112, first paragraph, as being non-enabling for a method to treat a subject having a lysosomal storage disease comprising a method wherein a composition comprising a p97 molecule covalently linked to a protein is actually administered to said subject/patient. Applicant respectfully disagrees for the following reasons.

The Examiner alleges that the application provides no evidence that a subject having a lysosomal storage disease can be treated with a composition comprising a p97-protein conjugate, citing the absence of a reduction to practice of the claimed method. The Examiner appears to be requesting *in vivo* data. Applicant respectfully submits that the *in vitro* data provided in the application enables the present claims. The present inventors have shown in Examples 1 and 2 of the specification that p97 is capable of targeting its conjugated partner into the lysosome of a cell. Further, p97 has been previously demonstrated to deliver compounds through the blood brain barrier (Jefferies et al. 5,981,194). We also include a Declaration under 37 CFR 1.132 by Dr. Wilfred Jefferies, which shows in paragraphs 8 and 9 that p97 is transcytosed across the blood brain barrier. In addition providing lysosomal enzymes that are lacking to the lysosome of a subject affected by a lysosomal storage disease is the basis for the traditional

treatment of intravenous enzyme replacement therapy and thus it is not necessary to show that lysosomal enzyme therapy itself is effective. The present application is an improved therapy in that it delivers the lysosomal enzyme to the lysosome of the cell. Since lysosomal storage diseases are characterized by a build up of undegraded "storage material" in the lysosome of a cell due to lack of enzyme, it is understood that providing the enzyme not only to the affected tissue but to the lysosomes in the cells of the affected tissue would be an effective therapy. Thus, the examples showing that p97 is capable of delivering its fused partner to the lysosome of the cell enables the present methods and compounds.

The Examiner notes at page 4 of the office action that a composition comprising p97 covalently linked to a protein was not made and only p97 linked to a fluorescent marker was shown. Applicant submits that the linking of the fluorescent marker is sufficient to show that p97 is able to deliver conjugated proteins to the lysosome of a cell. Further, the results provided in the Declaration at paragraph 10 show that various p97-N-iduronidase conjugates were made and results at paragraph 11 of the Declaration show that p97 and iduronidase co-localize in the lysosome of a cell.

Further, the Examiner alleges that "the delivery of the composition to the target site, clearance rate, degradation, the timing of delivery compared to chronological age, and other physiological factors have not been determined, let alone suggested". Applicant respectfully submits that such pharmacodynamic properties are not necessary for enablement and it would be unfair to demand such data as it would require that the Applicant begin clinical trials before submitting a patent application. With respect to the Examiner's statement that applicants have not demonstrated that any such fusion protein can be delivered to the target cell with intact activity, paragraph 12 of the Declaration by Dr. Wilfred Jefferies shows that p97 is degraded by Cathepsin D (a protease expressed in lysosomes) leaving the lysosomal enzyme intact and biologically active.

In view of the foregoing, we respectfully request that the rejection to the claims under 35 USC §112, first paragraph, be withdrawn.

35 USC §112, second paragraph

The Examiner rejected claims 9, 11 and 19 under 35 US §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In response, Applicant has amended claims 9, 11 and 19 to replace the "conjugate" with the "p97 molecule covalently linked to the protein". The amended claims 9 and 11 find antecedent basis in claim 1 and the amended claim 19 finds antecedent basis in claim 14.

In view of the above, Applicant respectfully requests that the rejection to the claims under 35 USC §112, second paragraph, be withdrawn.

35 USC §103(a)

The Examiner rejected claims 1-5, 7-14 and 16-20 under 35 USC §103(a) as obvious over the combined teachings from Lebowitz (USPGPB 2003/0072761 A1) and DeFrees et al. (US Patent 7,138,371 B1) in view of Jefferies et al. (U.S. Patent No. 5,981,194). We respectfully disagree with the Examiner for the reasons that follow.

The current application has an international filing date of January 10, 2003, and claims priority from a US provisional application filed on January 11, 2002. The Examiner cites DeFrees et al. as a primary reference for obviousness, and in particular, for disclosing the treatment of a lysosomal disorder with a p97 conjugate. DeFrees et al. has a filing date of November 5, 2002, which is after the present application's priority date. Applicant notes that DeFrees et al. claims priority to a number of provisional applications as stated on page 1 of the issued patent:

> This application is a continuation of copending PCT/US02/32263, filed Oct. 9, 2002; Provisional Patent Application No. 60/407,527, filed Aug. 28, 2002; Provisional Patent Application No. 60/404,249, filed Aug. 16, 2002; Provisional Patent Application No. 60/396,594, filed Jul. 17, 2002; Provisional Patent Application No. 60/391,777, filed Jun. 25, 2002; Provisional Patent Application No. 60/387,292, filed Jun. 7, 2002; Provisional Patent Application No. 60/334,233, filed Nov. 28, 2001; Provisional Patent Application No. 60/334,301, filed Nov. 28, 2001; Provisional Patent Application No. 60/344,692, filed Oct. 19, 2001; and Provisional Patent Application No. 60/328,523, filed Oct. 10, 2001.

Applicant submits that only four of the above priority applications predate the priority date of the present application, **January 11, 2002**:

> Provisional Patent Application No. 60/334,233, filed Nov. 28, 2001
> Provisional Patent Application No. 60/334,301, filed Nov. 28, 2001
> Provisional Patent Application No. 60/344,692, filed Oct. 19, 2001
> Provisional Patent Application No. 60/328,523, filed Oct. 10, 2001

The applications were only available in pdf form and were not keyword searchable. However, a review of the four documents did not find any reference to a method to treat a lysosomal storage disease nor any references to p97, melanotransferrin, Hexosaminidase A, Sandhoff disease or a table similar to "Table 4" in the issued patent (as specifically cited by the Examiner). In view of the foregoing, the earliest date of disclosure of the relevant section of DeFrees et al. is after the priority date of the present application and thus, Applicant respectfully submits that it appears that DeFrees et al. is not citable under 35 USC 103(a).

However, even if it were citable, Applicant respectfully submits that the DeFrees et al. disclosure would not render the present claims obvious. The Examiner points to paragraph 1222 which discloses the use of transferrin conjugated to an enzyme for

treatment of a lysosomal storage disease. The disclosure further states that other targeting agents related to transferrin can be used including melanotransferrin among others. However, transferrin is different from melanotransferrin with only 20% identity between the proteins. Further, it is known that transferrin is unable to efficiently cross the blood-brain-barrier (see, for example, Demeule et al. 1992 attached). Thus, it is unlikely that transferrin would be able to treat lysosomal storage diseases and therefore, it would not be expected that a protein only somewhat related to transferrin would work. Therefore, Applicant submits that the DeFrees et al. disclosure of melanotransferrin conjugates for treating lysosomal storage disorders would not amount to an enabling disclosure and thus should not be prior art to this application.

Further, the present claims require that the p97-conjugate be delivered to a lysosome of a cell. There is no disclosure that the conjugates of DeFrees et al. would deliver an enzyme to a lysosome in a cell.

The deficiencies in DeFrees et al., even if citable, are not remedied by Lebowitz et al. or Jefferies et al. The cited references together fail to suggest delivering p97-conjugates to a lysosome in a cell.

Lebowitz et al. merely teaches that Sandhoff disease is the result of the absence or defect in the presence of beta-hesoxaminidase. Applicant does not dispute that this was known in the art.

As stated in the previous response, Jefferies et al. teaches that p97 can be used to transport therapeutics across the blood brain barrier. Jefferies discloses that such therapeutic agents could be used to treat neurodegenerative diseases or tumors of the brain. Jefferies et al. does not disclose or suggest that p97 could deliver therapeutic agents into a lysosome in a cell. The reference provided in Jefferies, column 101/102, is directed at claim 6 of the issued patent which relates to a method of diagnosing or monitoring Alzheimer's disease by detecting p97 in a sample from subject. As stated in the previous response, **Alzheimer's disease is not a lysosomal storage disease.**

Based on the combined teachings of DeFrees et al. (if citable), Lebowitz et al. and Jefferies et al., one of skill in the art would **not** have a reasonable expectation that p97 could be used to target therapeutic agents to a lysosome. The ability of p97 to transport agents across the blood brain barrier is by transcytosis, wherein the agent is transported across the endothelial cells that form a barrier to a brain. Based on that mechanism of action, one could not predict whether or not p97 could also deliver agents into the lysosomes.

In view of the foregoing, we respectfully request that the objection to the claim under 35 USC §103 be withdrawn.

The Commissioner is hereby authorized to charge any fee (including any claim fee) which may be required to our Deposit Account No. 02-2095.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, she is kindly requested to contact the undersigned by telephone at (416) 957-1678 at her convenience.

Respectfully submitted,

Christopher M. Starr et al.

By _____

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